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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,864	DUDEK ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *4,6-16 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,17,21 and 22* is/are rejected.

7)☒ Claim(s) *17,21 and 22* is/are objected to.

8)☒ Claim(s) *1-22* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/16/02; 10/27/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-9, 17, 18 and 21-22, in the reply filed on 9/14/2005 is acknowledged.

The traversal is on the ground(s) that the inventions of Groups I and II are directed to overlapping subject matter. Applicants contend that although the inventions of Groups I and II are classified in different subclasses, the searches of the inventions of Groups I and II are co-extensive and can therefore be examined simultaneously without significant additional burden. Applicants also submit for the record that the inventions of Groups III and IV are classified in the same class and subclass and therefore could be examined simultaneously without undue burden.

This is not found persuasive because consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof; (B) a separate status in the art when they are classifiable together; or (C) a different field of search. These criteria were met in the above restriction. Although Groups I and II are in the same class, they are different subclasses and each method has a distinct goal and each requires distinct method steps that are not required by the other methods. A search for one of the methods of Group I or II would constitute a different search than that of a search for the other method. A search of the method of tumor therapy comprising administration of a hedgehog antagonist of Group I would constitute a different search from the method of determining a treatment based on levels of *gli* expression levels in a sample of Group II. Thus Groups I and II require divergent searches and to search both inventions would be burdensome. Furthermore, for the record, a search of one of the methods of Group III or IV would constitute a different search than that of a search for the other method. A search of stimulating surfactant production in a lung cell of Group III by contacting the cell with sufficient hedgehog antagonist constitutes a different search from the method of stimulating lamellated body formation in a lung cell by contacting the cell with sufficient hedgehog antagonist. Thus Groups III and IV require divergent searches and to search both would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-16, 19, and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/14/2005.

Applicant's election of the species of 1) colon cancer and 2) hedgehog antibodies in the reply filed on 9/14/2005 is acknowledged.

Claims 4, 6-9 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1-3, 5, 17, 21 and 22 are under consideration, as they read upon the elected species of colon cancer and hedgehog antibody.

Information Disclosure Statement

The information disclosure statements (IDS) submitted 12/16/02 and 10/27/2003 have been fully considered by the examiner. However, as References AC, AD, AE, AF, AG and AH of the IDS of 12/16/02 are U.S. patent applications or provisional applications and are not true publications with a publication date, they are not fully in compliance with 37 CFR 1.97 and thus have been crossed off the IDS and will not be printed on the face of any patent issuing from the instant application. However, the Examiner has considered these references. On the PTO-892 form accompanying this Office Action the Examiner has listed U.S. Patent No. 6545005, which corresponds to Application No. 09/663835 (Reference AC) and U.S. Patent No. 6552016, which corresponds to Application No. 09/688018 (Reference AF). It is noted that Applications Nos. 09/685244 (Reference AD), 09/687800 (Reference AE), 09/688076 (Reference AG) have neither issued as a U.S. Patent or Patent Application Publication. It is noted that Application 60/308449 (Reference AH) is a provisional application and therefore has not been published.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. Specifically, the Declaration filed 10/15/01 is defective because it was not executed in accordance with either 37 CFR 1.66 or 1.68. The Declaration is not signed by any of the inventors. A Pre-Exam Formalities notice was mailed to Applicants 12/6/01 indicating that the declaration was unsigned. However, a signed copy of the declaration has not been received.

Claim Objections

Claim 17 is objected to because the claim encompasses non-elected inventions and non-elected species.

Claim 21 is objected to because it uses the phrase "decrease the grow" in line 2. It is suggested that Applicants intended to use the phrase "decrease the growth".

Claim 22 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 21 is drawn to a method of treating a tumor comprising administering a hedgehog antagonist. This meets the definition of the phrase "cancer treatment regimen" as used in claim 22. Therefore, claim 22 does not further limit parent claim 21.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 17, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using a hedgehog

antibody 5E1, or cyclopamine, to inhibit unwanted cell proliferation of a pancreatic, bladder, colon, prostate, lung, or colon cancer cell line overexpressing the gli1 or Shh genes, either 1) in vitro or 2) subcutaneously injected in a mammal, does not reasonably provide enablement for other methods of inhibiting unwanted cell proliferation, including other forms of in vivo treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of inhibiting unwanted cell proliferation. The claims are directed to a broad genus of methods that encompasses any type of cell expressing a gli gene or a hedgehog gene, in any location (e.g., in vitro or in vivo), and any type of hedgehog antagonist. However, the specification provides limited teachings regarding whether or not the claimed methods will work to inhibit unwanted cell proliferation. The specification teaches (pg 153-156) that high levels of gli1 expression (as compared with "non-proliferative" cells) can be found in some tumors of the prostate, lung, and breast (e.g., "6 out of 15 prostate cancer samples all showed strong gli1 expression"; see pg 153). The specification further teaches that the gli1 and sonic hedgehog (Shh) genes are overexpressed in some bladder tumors as compared with normal bladder (pg 161). The specification further teaches that the anti-Shh antibody 5E1 inhibits tumor growth in nude mice injected with the bladder, colon or pancreatic cancer cell lines (pg 163; pg 171-174). The specification further teaches that 5E1 can block the ability of prostate cancer cells to induce the hedgehog pathway in normal cells, presumably by blocking secreted Shh (pg 166). The specification further teaches that the Shh gene and protein are expressed "in a wide range of both normal and

hyperproliferative tissues" and "further analysis is needed to ascertain, for a given tissue type, the differences in the level of hedgehog expression between normal and hyperproliferative tissue" (pg 170). The specification further teaches that the growth of a non-hedgehog expressing colon cancer cell line is not inhibited by 5E1 (pg 175).

With respect to colon cancer (which is the elected species of unwanted cell proliferation under consideration), the specification teaches that an anti-hedgehog antibody (5E1) "significantly decreases tumor size, weight, and rate of growth in comparison to that of mice treated with PBS (Figures 36 and 37; see pg 152-153). The tumors referred to here are tumors created in nude mice by subcutaneously injecting tumor cell line(s), and the 5E1 antibody was administered subcutaneously. The specification provides no other teachings regarding the use of hedgehog antagonists in treating colon cancer. The specification does not teach any other examples of in vivo treatment of colon tumors. The claims lack enablement for the full scope of in vivo treatment of unwanted cell proliferation. While Applicants examples demonstrate enablement of subcutaneously implanted cancer cell lines, they do not provide enablement for treatment of "native" tumors, for the following reasons:

1) The relevant art cautions that the subcutaneous microenvironment is different from that of the colon environment, and that orthotopic sites (i.e., in the colon) are necessary. Heijstek teaches, "a major disadvantage is that the subcutaneous (ectopic) microenvironment greatly differs from that of the colon or the liver. Interactions between the host environment and the tumor graft determines tumor cell expression profiles, the levels of growth factors and nutrients, as well as tumour angiogenesis and metastatic behavior...Orthotopic and ectopic organ environments differentially influence the sensitivity of tumor cells to chemotherapeutics" (see pg 20 of Heijstek et al, 2005. Dig Surg. 22: 16-25). Kobaek-Larsen teaches: "Whether to use nude or SCID mice is a difficult decision to make. Subcutaneous implantation of cell lines in both mice strains results in high incidence of tumor growth. However, the subcutaneous micro-environment is different from the original colonic environment, which is a disadvantage...Orthotopic implantation of colon cancer cell lines may solve the problem

of the "wrong" location of the metastases" (see pg 22 of Kobaek-Larsen et al, 2000. Comp Med. 50(1): 16-26).

2) Furthermore, the relevant art cautions that cancer cell lines are not necessarily representative of in vivo derived tumor cells. Kobaek-Larsen teaches, "Cell lines are highly selected cells, usually monocultures, which have the ability to grow in vitro. Furthermore, cell lines are far away from their origin, due to multiple cell divisions and animal passages. Therefore, tumor cell lines may not be representative of in vivo derived tumor cells. When working with cell lines, it is considered essential that the characteristics of the cell lines be examined and described in detail...Instead of using highly selected cell lines, transplantation of intact tumor tissue can be performed to avoid disruption of tissue integrity and change of cell characteristics" (see page 22).

3) Furthermore, with respect to treating tumors, it is unpredictable whether or not a hedgehog antagonist, e.g., an antibody, that inhibits a subcutaneous tumor comprised of a colon cancer cell line would also inhibit a tumor in the colon. As mentioned above, the microenvironment of the colon is different than the subcutaneous microenvironment. Furthermore, it is not predictable whether or not an antagonist that functioned subcutaneously could be delivered to the colon such that it would treat a tumor located there. With respect to the use of antibodies in treating colon cancer, the relevant art teaches that at the time the invention was made few antibodies "capable of targeting rapidly and efficiently to solid tumors have been identified. The main reasons for this are based on the inherent pharmacokinetics and physiology of IgG, the immunoglobulin molecule. Factors that may limit targeting potential include accessibility of the tumor antigen, and antibody affinity, molecular size and metabolism" (see Abstract of Welt et al, 1999, Semin Oncol. 26(6): 683-90.)

The claimed invention is also not enabled for the full scope of the following:

1) The term "a gli gene" is directed to a genus of genes, e.g. gli1, gli2, or gli3. However, Applicants have only shown overexpression of the gli1 and Shh genes in cancer cells. The relevant art teaches "GLI2 and GLI3 do not appear to be consistently expressed in prostate cancer cells" (see pg 12565 of Sanchez et al, 2004. PNAS. 101(34): 12561-12566).

2) The term hedgehog antagonist encompasses any compound that antagonizes any gene or protein of the hedgehog pathway (e.g., Shh, gli1, gli2, gli3, patched, smoothened, etc.). However, Applicants have not provided any examples of hedgehog antagonists that actually function to inhibit unwanted cell proliferation, other than the 5E1 antibody and the compound cyclopamine (which is well known in the art as a hedgehog pathway inhibitor). It is not predictable whether or not other antagonists could function to inhibit unwanted cell proliferation.

3) With respect to claims 21 and 22, the claims encompass a method of tumor treatment wherein gene expression is not measured. As Applicants have shown (pg 153), many tumors do not express the gli1 gene at any level different than non-proliferative tissue. Therefore these claims encompass treatment of tumors that would not be treatable with a hedgehog antagonist, and are therefore not enabled.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification whether or not the methods of the present invention could be used to treat a tumor in the colon of a patient. One of skill in the art would need to engage in undue experimentation in order to determine whether or not the hedgehog antagonist would actually work to treat a tumor in the colon. There are no examples of treating a tumor in the colon. Thus the specification fails to teach the skilled artisan how to use the method for treatment without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the method for the above stated purpose.

Due to the large quantity of experimentation necessary to determine whether or not a hedgehog antagonist could be used to treat colon cancer, including the quantity hedgehog antagonist to be administered, the most effective administration route, and the duration of the treatment; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; and the unpredictability of the effects of the hedgehog antagonist *in vivo,* undue experimentation would still be required of the skilled

artisan to make and/or use the claimed invention in its full scope. What Applicant has provided is a mere wish or plan and an invitation to experiment.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-3, 5, 17, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, paragraph 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of. The claims are genus claims because the claims are directed to methods using a genus of compounds encompassed by the term "hedgehog antagonist". The specification teaches that preferred embodiments of the hedgehog antagonist are a group consisting of a small molecule having a weight less than 2000 daltons, a hedgehog antibody, a patched antibody, a smoothened antibody, a mutant hedgehog protein, an antisense nucleic acid, and a ribozyme. However, the specification does not limit the term to any particular compound. Therefore, the term "antagonist" could pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetics, transformed cells, radiation, cyclic peptides, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known and unknown compounds.

This genus is highly variant because a significant number of structural differences between genus members are permitted. The claims do not require that the polypeptides possess any particular conserved structure or function, or other disclosed

distinguishing feature other than the ability to antagonize "hedgehog" (which could be the hedgehog protein or any other component of the hedgehog pathway, e.g., Shh, patched, smoothened, gli1, etc). The instant specification fails to describe the entire genus of hedgehog antagonists that will work with the claimed inventions.

From the specification, it is clear that Applicants has possession of method of inhibiting proliferation of several cancer cell lines (e.g., prostate or colon) that is subcutaneously injected in a mammal, by using a hedgehog antibody (e.g., 5E1). The specification also discusses cyclopamine, which the relevant art also appreciates as a hedgehog pathway antagonist. Applicants do not describe any hedgehog antagonists that actually work to inhibit proliferation of tumor.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of hedgehog antagonists to be used in the claimed methods. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish antagonists in the genus are missing from the disclosure. There is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the antagonists encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying

characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of hedgehog antagonists that would work to inhibit proliferation of cancer cells, or treat cancer, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only method of using a hedgehog antibody 5E1, or cyclopamine, to inhibit unwanted cell proliferation of a pancreatic, bladder, colon, prostate, lung, or colon cancer cell line overexpressing the gli1 or Shh genes, either 1) in vitro or 2) subcutaneously injected in a mammal, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5, 17, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "effective" in claim 1 is a relative term which renders the claim indefinite. The term "effective" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "effective" renders indefinite the amount of hedgehog antagonist to be administered.

The term "sufficient" in claim 21 is a relative term which renders the claim indefinite. The term "sufficient" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "sufficient" renders indefinite the amount of hedgehog antagonist to be administered.

Claims 2, 3, 5, 17, 22 are rejected for depending from an indefinite claim.

Claims 1-3, 5, 17, 21 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Claims 1-3, 5 and 17 are drawn to determining "whether cells overexpress a gli gene". The claims are missing the essential step of measuring gli gene expression in "reference" cells (e.g., non-tumor cells) and comparing the gli gene expression in order to determine if the test cells (e.g., potential tumor cells) have gli gene overexpression.

Claims 21 and 22 are missing the essential steps of determining whether the tumor cells overexpress the gli gene.

Claim Rejections - 35 USC § 102(a)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3 and 17 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Taipale et al, 2000. Nature 406: 1005-1009.

Taipale teaches that murine fibroblasts lacking *patched* overexpress the *Gli* gene (see pg 1006 and Supplementary Figure 2B). Taipale further teaches that growth of response-activated cells in low serum or growth agar reveals neoplastic transformation (see pg 1008). Taipale further teaches that the compound KAAD-cyclopamine inhibits growth of murine fibroblasts lacking *patched* in low serum. The terms "unwanted cell proliferation" and "cancer" as used in the claims encompass in vitro neoplastic growth. Page 8of the instant specification teaches that cyclopamine is encompassed by the term "hedgehog antagonist". Cyclopamine-KAAD has a molecular weight of 698 daltons, and therefore meets the limitation of a "small molecule having a molecular weight less than 2000 daltons". Therefore, Taipale teaches a method of inhibiting unwanted cell proliferation that clearly anticipates claims 1-3 and 17.

Claim Rejections - 35 USC § 102(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Baxter et al, U.S. Patent No. 6,545,005, published 4/8/2003, filed 9/15/2000 and claming priority to 9/16/1999.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Baxter et al teaches "The present invention makes available methods and reagents for inhibiting aberrant growth states resulting from activation of hedgehog signaling pathway...by contacting the cell with an agent, such as a small molecule, in a sufficient amount to reverse or control the aberrant growth state..." (col 6, lines 5-10). Baxter further teaches "Many other tumors may, based on evidence such as involvement of the hedgehog pathway in these tumors, or detected expression of hedgehog or its receptor in these tissues during development, be affected by treatment of the subject compounds. Such tumors include...tumors resulting from gli1 amplification (e.g., glioblastoma, sarcoma, etc.)" (column 45, lines 4-12).

Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Scott et al, U.S. Patent No. 6, 429, 354, published 8/6/2002 and filed 8/22/1997.

Scott teaches determining whether or not a cancer cell has a mutation in the *patched* gene (ptc). Specifically, Scott teaches "we have observed somatic mutations in the ptc gene in a variety of sporadic tumors" (col 4, lines 62-63). Scott further teaches that the both "ptc and Gli genes were strongly transcribed in the brain tumors but not in surrounding tissues" (col 33, lines 52-53 and Fig 7). Scott further teaches that gli is a patched-dependent gene "whose level of expression is regulated at least in part by the presence of a patched protein in the cell..." (col 7, lines 53-58). Therefore, determining whether or not cancer cells have a mutation in the *patched* gene inherently determines whether the cells overexpress a gli gene. Scott further teaches "The role of ptc as a tumor suppressor indicates that agents which mimic its function, in terms of transmembrane transport of molecules, transcriptional downregulation, etc., will inhibit the process of oncogenesis" (col 16, lines 58-62). An agent that that mimics ptc function

meets the definition of a "hedgehog antagonist". Therefore, Scott teaches a method of determining whether cells overexpress a *gli* gene and contacting the cells with amount of the hedgehog antagonist effective to inhibit oncogenesis, which is cell proliferation. Therefore, Scott anticipates claim 1.

Claim 2 limits the gli gene to gli1. The gli gene taught by Scott is alternately known as gli1; therefore, Scott anticipates claim 2.

Claim 3 limits the unwanted cell proliferation to cancer. As described above, Scott teaches inhibiting oncogenesis of cancer cell, and therefore anticipates claim 3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Scott et al, U.S. Patent No. 6, 429, 354, published 8/6/2002 and filed 8/22/1997.

Claim 5 encompasses a method of inhibiting colon cancer.

As summarized above, Scott teaches a method of inhibiting proliferation of cancer cells that overexpress a gli gene. Scott further teaches that a ptc mutation was found in a colon cancer line (col 39, line 22). As described above, a mutation in the ptc gene would inherently cause overexpression of the gli gene. Scott does not teach a method of inhibiting proliferation of a cancer cell directed to the species of colon cancer.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to apply the general teachings of Scott regarding inhibition of proliferation of cancer cells to the specific species of colon cancer. The person of ordinary skill in the art would be motivated to do so because Scott teaches a colon cancer cell line with a ptc mutation that inherently has overexpression of the gli gene, and Scott teaches that agents that mimic patched function will inhibit oncogenesis of cells with patched mutations. The person of ordinary skill in the art would have expected

success because Scott provides general teachings that apply to any species of cancer overexpressing gli, and provides an example of a colon cancer overexpressing gli.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5, 17, 21 and 22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 17, 21 and 22 of copending Application No. 10/652298. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claim 1 is drawn a method of inhibiting unwanted cell proliferation of cells overexpressing the gli gene by contacting them with a hedgehog antagonist. Claim 2 limits the gli gene to gli1. Claim 3 limits the unwanted cell proliferation to cancer and claim 5 is drawn to species of cancer. Claim 17 is drawn to species of hedgehog antagonist. Claim 21 is an independent claim drawn to a method for treating a tumor in a patient by giving the patient a hedgehog antagonist. Claim 22 limits the administration to part of a cancer treatment regimen.

Claim 1 of application '298 is drawn to a method of inhibiting "one of unwanted growth, proliferation or survival" of cells expressing the gli gene by contacting them with a hedgehog antagonist. Claim 1 of the instant application is obvious over claim 1 of '298

for the following reasons: 1) The goal of instant claim 1 is one of three possible goals set forth in claim 1 of '298; 2) The method steps of instant claim 1 and claim 1 of '298 are nearly identical. The only difference is that instant claim 1 is directed to determining whether cells overexpress gli and claim 1 of '298 is directed to determining whether cells express gli. Therefore, the method steps of claim 1 of '298 are broader, because they encompass any expression of the gli gene, whether it is overexpression, underexpression, or the same expression. However, the portion of the specification of application '298 that is directed to this claim teaches "overexpression of a gli gene indicates that treatment with a hedgehog antagonist is appropriate" (see pg 8). Therefore, claim 1 of the instant application is obvious over claim of '298 in view of the teachings of the specification regarding the claimed method.

Furthermore, claims 2 and 3 of the instant application are obvious over claims 2 and 3 of '298 as each set of claims recites the same set of dependent limitations.

Claim 5 of application '298 depends from claim 3 and limits the cancer to one of twelve species. Claim 5 of the instant application is obvious over claim 5 of '298 because each of the five species recited in instant claim 5 are present in claim 5 of '298.

Claim 17 of application '298 limits the hedgehog antagonist to the same species as recited in instant claim 17. Instant claim 17 is obvious over claim 17 of '298 because the parent claims are obvious (for the reasons cited above) and each of the dependent claims recite the same limitations.

Claim 21 of application '298 is drawn to a method of treating a tumor in a patient by administering a hedgehog antagonist sufficient to decrease growth, proliferation or survival of the tumor, wherein the tumor expresses at least one of a hedgehog gene or a gli gene. This differs from instant claim 21 in that instant claim does not recite the limitation "wherein the tumor expresses at least one of a hedgehog gene or a gli gene" and instant claim 21 limits the tumor to one of six species. However, instant claim 21 is obvious over claim 21 of '298 because the relevant portion instant specification teaches "the present invention makes available methods and reagents for inhibiting undesirable growth states that occur in cells with an active hedgehog signaling pathway" (page 8) Cells with an active signaling pathway must express both the hedgehog gene and the

gli1 gene. Furthermore, application '298 teaches on page that each of the species of cancer recited instant claim 21 are exemplary forms of cancer which can be treated with the claimed method.

For these reasons, it would have been obvious to the person of skill in the art to modify the claims of application '298 as recited in the instant claims. The person of ordinary skill in the art would have been motivated to make the modifications as recited in the instant claims because as outlined above, all of the changes are either specifically exemplified as alternatives in the claims of '298, or are taught by the specification of '298 as exemplary embodiments of the methods.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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